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A model for reading morphogenetic gradients: Autocatalysis and competition at the gene level

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ABSTRACT **How are morphogenetic gradients interpreted in terms of embryonic gene transcription patterns within a syncytium such as the *Drosophila* blastoderm? We propose a hypothetical model based on recent findings in the molecular biology of transcription factors. The model postulates a morphogen which is itself a spatially distributed transcription factor M or which generates a distribution of such a factor. We posit the existence of an additional, zygotically transcribed "vernier" factor V. M and V form all possible dimers: MM, MV, and VV. These are differentially translocated to the nuclei and bind with various affinities to responsive elements in the V promoter, thereby contributing to activation/inactivation of V transcription. We find four generic regimes. In order of complexity, they are as follows: (*i*) MM activates V; the M gradient gives rise to a sharp transcriptional boundary for V and to a secondary gradient in the concentration of protein V; (*ii*) MV activates V; a sharp boundary in transcription and distribution of V arises; (*iii*) MM and MV compete for binding; a stationary stripe of active V transcription is generated; (*iv*) MM and VV are in competition; a stripe of V transcription moves from one end of the embryo toward the other and may stop and/or dwindle at an intermediate position. Tentative interpretations in terms of *Drosophila* genes such as bicoid and hunchback are presented.**

Early in the history of embryology, gradients of morphogenetic substances were postulated to direct the development of form (1–3). Yet, it has only recently been established that gradients of diffusible substances are involved in the unfolding of gene expression patterns along the axes of the *Drosophila* syncytial blastoderm. The protein products of the developmental genes bicoid (4) or dorsal (5), for instance, constitute two of the initial, syncytium-wide maternal gradients, whereas hunchback (6) forms a later, more localized spatial distribution (7) whose origin appears partly zygotic.

The best studied morphogens to date are bicoid and dorsal. In the case of bicoid it has been shown, for instance, that a factor of 2 in concentration suffices to switch on the hunchback gene (8, 9), and that bicoid at various levels can indeed give rise to activation of different genes (10, 11).

The case for diffusible morphogens in cellularized embryos is less clear-cut (12, 13). Cell–cell short-range interactions probably play an important role. Still, in the chicken embryo limb bud, retinoic acid appears to be a plausible candidate for the role of diffusible morphogen (14–16).

The effects of morphogens are mediated by factors which exert control over gene transcription. The molecular biology of these factors is becoming elucidated. One salient feature now emerging is that many if not the majority of eukaryotic transcription factors are effective as oligomers. Thus, the members of the Fos–Jun (17), Myc–Max (18), MyoD–E1 (19), or achaete-scute (20, 21) families act as homo- or heterodimers. Retinoic acid carries out its function through binding to nuclear receptors of the steroid receptor family (22), which it activates by allosteric effects (23), inducing them to form a variety of dimers among themselves. Another example of significant morphogenetic importance concerns the worm *Caenorhabditis elegans*, where the homeoproteins UNC-86 and MEC-3, which specify neuronal cell fate, apparently do so by way of formation of heterodimers with increased DNA-binding stability with respect to the monomers (24). The combinatorial complexity which results from dimer formation is further increased by the composite structure of the genomic promoter/enhancer sites, with their variety of high- and low-affinity components (5).

Transcription factors control, in addition to structural genes, transcription of their own and other genes coding for transcription factors. Thus, many transcription factors bind to their own promoter elements, leading to autoregulation. For instance, myogenic factors of the helix–loop–helix family (Myo-D, myogenin, Myf-5) positively regulate transcription of their own genes (25). In *Drosophila*, two developmental genes, gooseberry and wingless, form a mutual autoregulatory loop possibly involving engrailed as well (26). The *Pax* gene family (27) plays an important role in both *Drosophila* and vertebrate development, being involved in particular in central nervous system morphogenesis (28); its members encode transcription factors with a rich variety of DNA–protein and protein–protein interactions, consistent with the above picture of oligomer formation. Furthermore, it appears plausible that the *pax* (*zf-b*) and *wnt-1* genes engage in mutual autoregulatory interactions.

In the regulatory processes mentioned, control of nuclear translocation is often crucial: for example the *Drosophila* developmental gene dorsal exhibits a gradient of nuclear localization along the dorsoventral axis (29). Also, dorsal is homologous to T-lymphocytic NF-κB, which is downregulated by IκBα (30) through cytoplasmic sequestration.

A critical component of morphogenetic models (3, 31–33) is the mechanism for interpreting morphogen concentrations. Based on the above discussion, we propose in this paper a theoretical model for gradient reading which extends former attempts to model gene transcription at the motor endplate (38). Oligomer formation and autocatalysis are the crucial assumptions.

Biological Assumptions

We assume that the morphogen M is a transcription factor or that it activates such a factor, which forms a preestablished gradient (e.g., of maternal origin) (6, 9–11, 34). A second, zygotically expressed transcription factor V is introduced, which may form, together with M, all possible homo- or heterodimers: MM, MV, and VV. V will be the "vernier" molecule responsible for fine gradient reading (35). The major premises of the model are as follows.

(*i*) In the initial state, an exponential gradient of morphogen protein is established along one axis of the embryo. The gradient may be the product of a maternal mRNA distribution (bicoid); or it could result from

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the allosteric activation of a nuclear receptor by a diffusible ligand (retinoic acid); alternatively, it might be established at least in part through a relatively independent morphogenesis process (hunchback).

(*ii*) The morphogen is a transcription factor, or activates a transcription factor.

(*iii*) The gradient is read by a zygotically expressed transcription factor V, through dimerization of V with M; in addition to this fundamental reaction, VV and MM homodimer formation may occur.

(*iv*) The sequence (gene → V → MV → promoter → gene) composes an autocatalytic loop.

(*v*) Modulation of the loop efficiency happens through promoter sites with different affinities or through the differential rates at which transcription factors are translocated to the nucleus and competition among factors.

(*vi*) The vernier molecule V may lie at the start of a regulatory cascade (36) and thus control batteries of structural genes.

We now describe briefly the possible evolutions of M and V concentrations. Formal proof will be offered in the next sections. If transcription of V is controlled by MM dimer, a secondary V gradient is generated in register with the initial one. If it is the MV complex which promotes V expression (autocatalysis), a sharp V boundary appears. In both cases, uniform transcription of V becomes limited to an "active" embryonic region where M concentration lies above a threshold. If M is scarce, dimerization with V depletes M where V is expressed and a diffusion of M into the active region ensues, stabilizing further the incipient pattern. Dimer competition or synergy may also occur: antagonistic effect of MM against MV for promoter binding hinders V expression at high M, leading to stripe formation, while competition among VV and MV may result in a transcriptional wave sweeping the embryo or part of it starting from the high-M extremity and ending where M decreases below a threshold.

Formal Model

The morphogen M is initially distributed according to an exponential gradient $M_0e^{-x/\lambda}$. It is not further transcribed in the embryo at the time the gradient is read, and it decays very slowly. The vernier factor V *is* transcribed, and we formalize its induced transcription in nucleus n by a genetic switch (37, 38). Transcription of V at first proceeds in a statistically uniform way. Once synthesized, however, V diffuses between cytoplasmic compartments and forms the MV complex, a positive regulator of transcription of the gene encoding V (VV dimer may form as well).

We study the embryo over two dimensions and divide it into 100 × 25 "boxes." Five hundred of these boxes, chosen at random, contain a nucleus (the precise values quoted are not critical). The concentration of M, V, MV, and (optionally) MM or VV obey straightforward discrete diffusion–reaction equations governed by mass-action laws for the formation and decay of dimers; the crucial term is the source term for V, present if the box ij contains a nucleus n, since the V gene may be transcribed with a probability P_n. P_n depends on the presence of transcription factors at the promoter binding sites, these sites being characterized by their respective affinities and synergistic/antagonistic interactions. We assume P_n to be a sigmoid function of promoter occupancy:

$$P_n = \frac{1-b-f}{2} \times \left[1 + \tanh \frac{\beta_1 MV^x + \beta_2 DD^y + (\beta_3 MV^z \cdot DD^t) - T}{Q}\right] + b, \quad [1]$$

where b is the basal transcription rate, f the transcription failure rate at high promoter occupancy, DD may be absent or stand for MM or VV homodimers as the case may be, T and Q are the threshold and width of the sigmoid, β_1 and β_2 are the promoter binding coefficients, and β_3 is a term best described as a synergistic dimer interaction if positive and an antagonistic dimer interaction if negative. β_1 is always zero or positive, ensuring in the latter case autocatalysis—i.e., a minimal synergy between M and V. The exponents x, y, z, and t describe the detailed kinetics of promoter response elements: we shall take them equal to 1 for simplicity, since our qualitative findings are essentially independent of their value. The reaction scheme and the notation are defined in Fig. 1 and the scheme has been solved on a digital computer. Approximate solutions for stationary states and their stability can be obtained analytically.

Results

At a given morphogen concentration, that is, at a given point x, transcription may be on, off, bistable (i.e., in a regime where transcription is either high or low, dependent on relative stability of the two states and sometimes on system history) or unstable (i.e., not settling into a stationary pattern). The existence and stability of on and off states can be determined analytically for simple cases (see *Appendix B* for analytical expressions). Accordingly, four distinct, generic regimes can be defined, corresponding to extended ranges of values in parameter space and yielding different behavior of the model. We have chosen parameters (see *Appendix A*) appropriate to obtain representative results for each of the

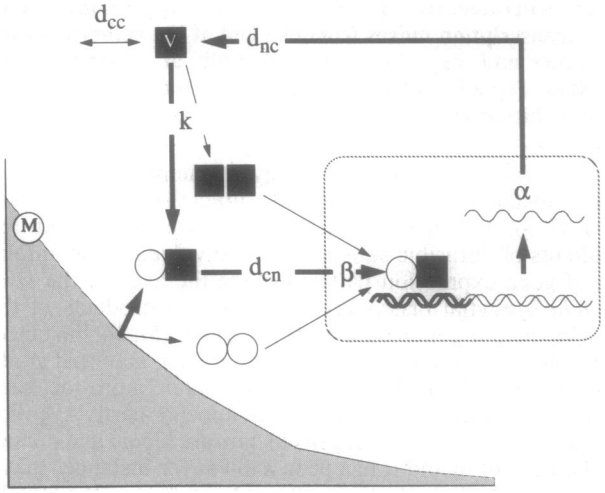

FIG. 1. The model. Morphogen M (circles) is initially distributed in a graded fashion. M, the autocatalytic vernier protein V (squares), their dimer MV, and (optionally) a homodimer DD (= MM or VV) all diffuse and react over a discrete two-dimensional space (lattice) of cytoplasm and nuclei. A nucleus is represented here (enclosed by a broken line). Diffusion toward and away from nuclei is not symmetrical. Thus, if there is a nucleus at position i,j, the net flux of, say, V from i,j to $i+1,j$ (cytoplasm) is $d^V_{c\to n}V_{i+1,j} - d^V_{n\to c}V_{i,j}$, where $V_{i,j}$ is the location-dependent V concentration. The dimerization reactions are M + V ⇌ MV which is always present, and one of the optional homodimerizations: M + M ⇌ MM or V + V ⇌ VV. All reactions take place according to mass-action laws and we denote the corresponding constants e.g. for MV formation and decay, $k^{\rightarrow}_{MV}$ and $k^{\leftarrow}_{MV}$, respectively. Transcription of the gene encoding V is under the control of the dimers located at a given nucleus and their competitive/cooperative interactions. The gene is turned on with sigmoid probability P_n as given in the text (see Eq. 1), dependent on promoter occupancy with relative binding affinity coefficients β_1 and β_2 and interaction coefficient β_3. When transcribed, the V gene gives rise to the production of α molecules of V per unit of time (for numerical values, see *Appendix A*).

four regimes, which are respectively MM- or MV-dominated, and MV–MM or MV–VV competition-regulated.

Smooth Gradient Reading by the MM Homodimer. To establish a boundary in the spatial concentration of a vernier molecule V, starting from a smoothly distributed M, cooperativity is needed (10). An interesting regime, in the context of dimer formation, is thus the simple one where MM homodimer promotes V gene transcription, which we denote as the MM → +V model. The results of a typical simulation of this model are displayed in Fig. 2, where we see that the final stable situation, starting from complete absence of V, is a graded distribution of this molecule, steeper than that of M. It is interesting that, in terms of transcriptional activity, the transition is sharp. Analytically, the position of this abrupt boundary is easily deduced as the location where concentration of M leads to a 50% chance for transcription being on—i.e., by equating Eq. 2 (see *Appendix B*) to 0. Thus, the gradient is read precisely in terms of gene activation patterns but defines a rather smooth protein distribution, suitable to play, for example, the role of a secondary morphogenetic gradient. In the discussion, we shall come back to this in the context of hunchback. As against this flexibility in concentration of the secondary gradient, understandable since V plays no role in transcription, the presence of V depends here entirely on M at all times and is in no way self-maintained.

Sharp Gradient Reading by the MV Heterodimer. We now turn to the pure MV → +V model, where the MV heterodimer controls positively the transcription of the V gene. Here the gradient of M is read reliably and sharply, both in concentration and in transcriptional intensity. No secondary gradient may arise. The boundary occurs at a threshold concentration, M_1. This is located, to a first approximation, at the point where M concentration is such that the V loop gain is 1; i.e., per unit of time, one molecule of V forms MV in such an amount that the transcription it induces will yield fresh V in just the quantity needed to balance decay (see *Appendix B* for analytical expressions). This reasoning neglects diffusion of all factors: if this is slow the resulting corrections are not appreciable. Dynamically, the V gene is switched on in nuclei starting from the high-M end, and transcription is progressively established as an "on-wave" all the way to the threshold value. A smooth M gradient is thus seen to lead from an initially uniform rate of basal expression of V to a sharp boundary (Fig. 3). In contrast to the situation illustrated in Fig. 2, however, a sharp boundary

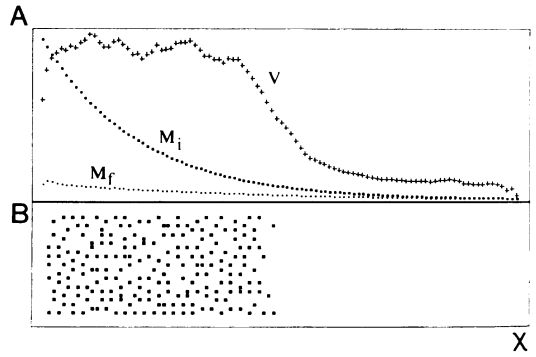

FIG. 2. Gradient reading by a cooperatively bound morphogen and generation of a secondary gradient. In this and subsequent figures, *A* displays protein concentrations, with the larger filled squares denoting the initial gradient of morphogen M_i along coordinate χ of the embryo, small squares its final (late times) concentration M_f, and crosses the final vernier distribution *V*. *B* represents nuclei in the simulated two-dimensional embryo. Only those nuclei are shown in which V transcription is turned on (filled squares) at late times. A sharp boundary is seen in the distribution of those nuclei. The protein V itself, however, shows a rather smooth distribution, which may be considered a secondary gradient.

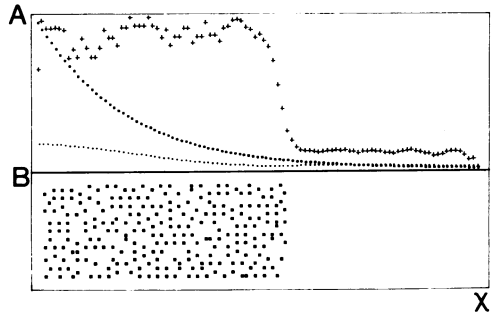

FIG. 3. Gradient reading by the autocatalytic vernier protein V. Transcription of the gene encoding V is induced by MV dimer, and this cooperativity gives rise to a sharp boundary in V expression. The boundary is at first located at that threshold M concentration, M_1, for which the amplification factor (gain) of the V regulation loop is precisely 1. Due to diffusion of the involved substances, it then moves somewhat toward the low-*M* region. When the morphogen is scarce, its depletion may result in a countergradient which reduces this later motion and stabilizes the boundary.

in V concentration is now apparent as well. On these figures one also notices that when M is scarce, its concentration diminishes appreciably as MV dimer forms in the active zone. Counterdiffusion of M toward that zone follows, stabilizing the exclusive expression of V there and leaving a very shallow final distribution of M. The scarce-M situation is favorable because the ultimate location of the boundary then depends less on the fine details of the initial M distribution than on the total quantity of M available on the high-M side of the embryo. This gives the phenomenon a quality reminiscent of embryonic induction (39), as will be considered in the *Discussion*.

MV–MM Interaction: Reading the Gradient at Two Levels and Forming a Stripe. In the presence of MM dimer competing for promoter sites with MV, band formation may result (Fig. 4). Indeed, if the competition is not too strong, the M_1 threshold will simply be brought up somewhat; but when M (and thus MM) concentration reaches a high enough value, $M = M_2$, negative interaction will cause the V-loop gain to drop again below 1, hence transcription will be switched off for $M > M_2$ (see *Appendix B*).

MV–VV Interaction: Formation of a Moving Stripe. Inhibition of V transcription by VV interacting negatively with MV will by itself lead to an essentially unstable or "chaotic" situation. If enough VV dimer forms, transcription stops, thus lowering the level of V and then that of VV, which in turn

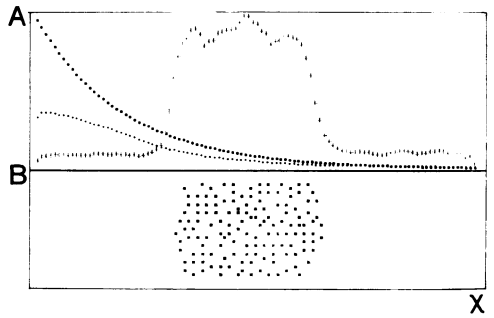

FIG. 4. Effect of MM homodimer formation. Double gradient reading by the vernier protein V is seen to occur. Here the action of the MV dimer (see Fig. 3) is antagonized at large M concentrations by the formation of abundant MM homodimer which competes with MV for promoter sites on the V gene, thereby reducing the V autocatalytic loop gain. At the M concentration M_2, where MM reduces this amplification factor below 1, V transcription is turned off once more (again, the latter threshold moves somewhat at later times due to diffusion effects).

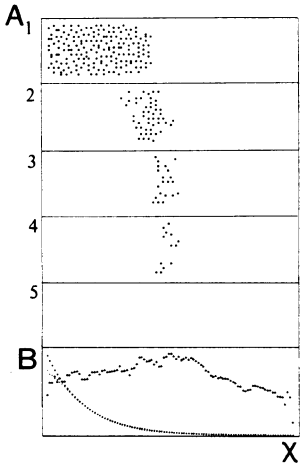

FIG. 5. Effect of MV—VV homodimer competition. A wave of V transcription is switched on by this phenomenon. Successive snapshots of the transcriptional state of the V gene are shown from top to bottom in A_1 to A_5: dots show where transcription is on. *B* displays the final distribution of transcription factors. In A_1 one sees how, initially, the gradient is read through MV formation (Fig. 3), creating a sharp boundary. Later, formation of VV occurs, competing with MV for promoter binding and reducing V transcription. Were this the sole effect of VV, the situation would be unstable, with quasi-random cycles of transcription being turned on or off as V (and VV) concentrations went low or high. If, however, VV, while reducing MV binding (and therefore MV efficiency), also has by itself a slight positive effect on V transcription, then a low V transcription rate will generate enough VV dimer to keep MV-mediated induction off. Transcription will thus progressively be reduced at one end of the embryo, while the initial boundary progresses due to diffusion of MV; the net result is a wave of transcription which stops at the point where MV goes below a threshold concentration.

will lift the inhibition, leading to a surge in transcription. A slight positive effect of VV alone on V transcription is needed to yield an interesting morphogenetic situation (Fig. 5). Then the presence of enough VV will suffice to establish V transcription, albeit at a low level. This quenches the instability. Instead, as the level of VV rises in the active zone, V transcription will go down without being turned entirely off, starting at the high-M (high-V) extremity. This will progress as an "off wave" through the active zone, until the location of the M_1 threshold is reached and high-level transcription dies out altogether. A race between the on wave and the off wave determines the exact place where this occurs.

Discussion

We have shown how a morphogen gradient may be read by formation with a vernier molecule of a dimer which promotes vernier transcription itself. This alone suffices to establish a sharp boundary located where morphogen concentration reaches a threshold. The combinatorial power of allowing for other dimerization reactions and competition among dimers for promoter sites leads to additional possibilities, such as stripe (40) or wave (41) formation, the occurrence of which is well documented.

The *Drosophila* hunchback gene and the well-characterized gap genes it controls can all be classified as transcription factors and are known to possess DNA-binding motifs of either zinc-finger type (42), steroid hormone receptor type (43), or helix–loop–helix type (7). They may thus interact in the fashion postulated by the model. For instance, the hunchback protein itself is a "secondary" morphogen, whose relatively graded distribution is partially generated by zygotic transcription: the bicoid protein seems indeed able to elicit hunchback expression with no need for specific cofactors, making this system a good candidate for the MM → +V model. As against such a simplistic interpretation, we note that there are hunchback-responsive elements in the hunchback promoter, making it possible that MV → +V or VV → +V components might be present as well.

Regulation of the *Drosophila* stripe 2 gene (44) involves bicoid–hunchback interactions, and elements responsive to both have been discovered in the Krüppel promoter (45) as well. This makes stripe 2 and Krüppel likely candidates for MV–MM model application.

We have predicted that, in the case of scarce morphogen concentrations, the actual determining factor for boundary location is the total amount of morphogen deposited assymetrically, rather than the exact gradient shape. If a dose of morphogen is synthesized on one side of the embryo, it will ultimately initiate transcription in a well-defined subregion, as observed in embryonic induction (39). Induction and gradient reading might thus appear as just two facets of a single phenomenon. It becomes possible to think in terms of a developmental hierarchy of more and more narrowly localized processes (7), starting from global gradients (bicoid and nanos) to regional (hunchback), and then to more local ones (the other gap proteins giant, knirps, and Krüppel). The hierarchy may go on with the pair-rule genes (46) and end with such localized cell–cell communications as illustrated in wingless–engrailed regulation (47) or in the eye, where the sevenless tyrosine kinase receptor (48) and its membrane-bound ligand boss (49) seem to interact directly (50).

In this work, nuclear localization of transcription factors was the major factor modulating transcription, but other control mechanisms are not precluded, and Eq. **2** can be used to sort out the relative influences of promoter affinities β and diffusion coefficients d in setting the thresholds.

Our simple morphogenetic model, taking into account the molecular biology of transcription factors, thus encompasses many known phenomena in gradient-mediated morphogenesis, suggesting a rational classification scheme for the possible generic outcomes of such processes and showing a rich potential in terms of experimental predictions.

Appendix A

The parameters common to all our computer runs have the following values: diffusion of monomers, $d_{c\to c} = 0.05$, $d_{c\to n} = 10^{-6}$, $d_{n\to c} = 0.005$; diffusion of dimers, $d_{c\to c} = 0.01$, $d_{c\to n} = 0.10$, $d_{n\to c} = 5 \times 10^{-5}$; transcription, $b = 0.1, f = 0.05, Q = 0.1, T = 0.2, \alpha = 0.02$. Parameters which may assume different values in Figs. 2–5 are shown below.

	$k_V^{\leftarrow}$	$k_{MV}^{\rightarrow}$	$k_{MV}^{\leftarrow}$	$k_{DD}^{\rightarrow}$	$k_{DD}^{\leftarrow}$	β_1	β_2	β_3	M_0	λ
Fig. 2	0.001	0	0	0.05	0.01	0	0.3	0	5.0	20
Fig. 3	0.001	0.15	0.15	0	0	0.6	0	0	5.0	20
Fig. 4	0.01	0.15	0.06	0.01	0.05	0.65	0	−1.0	10.0	20
Fig. 5	0.01	0.15	0.06	0.05	0.01	1.0	0.3	−1.4	10.0	30

Here $k_V^{\leftarrow}$ is the V decay constant and λ is given in units of the lattice spacing. For Figs. 2 and 4, *DD* = *MM*; for Fig. 5, *DD* = *VV*.

Appendix B

For abundant M, the condition for a stable V concentration is easily computed. We denote E the exponent in Eq. **1**. If $Q \to \infty$, E should be positive for the "on" solution and negative for the "off" one. The stationarity conditions for dimer formation, dissociation, and diffusion into the nucleus yield

$$V_s = \frac{P_s \alpha}{k_V^{\leftarrow}}$$

$$E_s = -T + MV_s\beta_1 \frac{\vec{k}_{MV}\, d^{MV}_{c\to n}}{\overleftarrow{k}_{MV}\, d^{MV}_{n\to c}} + D^2\beta_2 \frac{\vec{k}_{DD}\, d^{DD}_{c\to n}}{\overleftarrow{k}_{DD}\, d^{DD}_{n\to c}} + MV_sD^2\beta_3 \frac{\vec{k}_{MV}\, d^{MV}_{c\to n}}{\overleftarrow{k}_{MV}\, d^{MV}_{n\to c}} \frac{\vec{k}_{DD}\, d^{DD}_{c\to n}}{\overleftarrow{k}_{DD}\, d^{DD}_{n\to c}}, \quad [2]$$

where V_s denotes the stabilized concentration of V, D = either M or V_s, and P_s is either $P_{on} = 1 - f$ or $P_{off} = b$. Either the two solutions s = on and s = off exist (bistable case), or just one, or none (no stable state). We shall not present a full study but indicate briefly three situations of interest.

When only β_1 is nonzero, Eq. 2 is linear in M and E_{on} has one zero, at the M_1 threshold (see text). For $D = M$, $\beta_1 > 0$ and $\beta_2 < 0$, the equation is quadratic in M and there will appear two thresholds $M_2 > M_1$ between which the on state may exist; if $\beta_2 \approx 0$ and $\beta_3 < 0$ the situation is essentially the same with M_1 and M_2 the two positive roots of Eq. 2. For $D = V$, the novel aspect is the disappearance of stationary solution which occurs for β_3 sufficiently negative, as can be observed from Eq. 2; a dynamic phenomenon then develops (see text). Local stability analysis of all solutions is possible but yields complicated expressions.

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